Amendments to the Drawings:

Please delete Figure 7 from the Drawings.

REMARKS

In response to the Final Office Action mailed May 15, 2007, Applicants respectfully request favorable reconsideration of the above-identified application in view of the present Amendment and accompanying Request for Continued Examination. Claims 1-7, 17, and 18 are currently pending and under examination. By the present Amendment, claim 17 is canceled, and claims 1, 2, and 7 are amended to more specifically recite certain embodiments of the present invention. New claims 21 and 22 are added to recite particular embodiments of the presently claimed method. Support for the above amendments may be found throughout the specification as originally filed. No new matter has been added. The above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the amendments, claims 1-7, 18, 21 and22 are pending and under consideration in the application.

Objection to the Specification

The Examiner has objected to the specification for not containing a brief description of Figure 7. By the present Amendment, Applicants have canceled Figure 7, thereby obviating this basis of objection.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 1 stands rejected for allegedly being indefinite in lacking sufficient antecedent basis for the term "astrocyte." By the present amendment, claim 1 has been amended to recite "an astrocyte," which clarifies this term to indicate that it is not referring to a previously described astrocyte. Applicants submit that this basis of rejection is overcome by this amendment and respectfully request that the Examiner, therefore, withdraw this basis of rejection.

Claim 17 stands rejected for lacking insufficient antecedent basis for the term "said cells." Claim 17 is canceled by the present amendment, thereby obviating this basis of rejection.

Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-7, 17, and 18 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not being sufficiently enabled by the instant specification. More specifically, the Examiner indicates that the instant claims are interpreted to be treatment, but that the instant specification is not reasonable predictive for any particular treatment. Thus the instant claims are rejected as not being enabled for any particular therapy in humans.

Applicants respectfully traverse these bases of rejection and submit that the presently claimed methods are fully enabled by the instant specification. Specifically, Applicants submit that the instant specification teaches the skilled artisan how to make and use the claimed invention without undue experimentation.

As an initial matter, Applicants note that the claims have been amended to focus more specifically on certain embodiments of the presently claimed methods. For instance, the claims have been amended to recite that the cells are administered in one or multiple dosages of between about 10^5 and 10^{13} cells per 100 kg patient. Furthermore, claim 1 now recites that the human donor is syngeneic with the patient, and claim 2 recites that administration is by direct injection into the brain. Support for direct injection is provided, *e.g.*, on page 15, lines 11 and 12; support for the recited dosages is provided, *e.g.*, on page 29, lines 18-26; and support for the donor being syngeneic with the patient is provided throughout the specification and claim 2 as filed.

Applicants respectfully submit that while the instant specification does not provide working examples demonstrating the treatment of a neurological disease according to the presently claimed methods, the skilled artisan would appreciate that the instant specification provides sufficient guidance to practice for the skilled artisan to practice the presently claimed

methods with a reasonable expectation of success, without undue experimentation, particularly given the working examples of success in animal models of human disease provided in the instant specification.

As described in Example 7, the instant specification demonstrates that human MSCs isolated from normal brain and subsequently injected directly into rat brain successfully implanted and migrated to multiple sites within the rat brain and, furthermore, persisted in the rat brain after 5 to 72 days. Given this finding, the skilled artisan would appreciate that the presently claimed methods could be successfully employed to introduce MSCs directly into the human brain for therapeutic purposes, such as the treatment of neurodegenerative diseases or trauma to the CNS.

With respect to the Examiner's view that the use of rodent models is insufficient to demonstrate that the presently claimed methods could be successfully practiced in humans, Applicants disagree with this reasoning. Instead, Applicants submit that the larger scientific community believes that rodents are, in fact, suitable models for studying human biology and disease. For example, the Ungerstedt rat model of Parkinson's disease has been widely accepted for many years (Metz, G.A. *et al.*, *European Journal of Neuroscience* 22:735-744 (2005)). Accordingly, such rodent models must be considered reasonable predictive of the human model.

Regarding the Horn *et al.* reference cited by the Examiner, Applicants submit that this reference has little or no bearing on the presently claimed methods. Horn *et al.* is cited by the Examiner as teaching that transduction of hematopoietic cells in large animal models, rather than rodent models, is more predictive of human hematopoietic cell transduction efficiency. Applicants respectfully submit that this is not pertinent to the presently claimed methods, since they do not claim gene therapy methods. Nonetheless, Applicants do note that the issue of transduction efficiency has little or no bearing of the success of gene therapy methods when the cells are transduced *in vitro* and then the transduced cells are selected prior to administration to a patient.

In addition, results using hematopoietic cells cannot be properly analogized to the present methods, which are directed to bone marrow stromal cells, since such hematopoietic cells possess far less "stemness" than the presently recited bone marrow stromal cells (*see*, Savitz *et al.*, *NeuroRx®The Journal of the American Society for Experimental NeuroTherapeutics*, Vol. 1, pp. 406-414 at page 410, col. 2, last paragraph). In addition, it should be noted that Horn *et al.* should properly be considered as supporting the use of rodent models, since Horn *et al.* demonstrates that the side effect of oncoretroviral transduction in the X-SCID mouse model, namely leukemia, was recapitulated in 2 of 15 patients during human trials. Thus, the X-SCID mouse model was, in fact, reasonably predictive of the human therapeutic outcome.

Applicants further submit that Savitz *et al.* further confirm the predictive value of rodent models, when stating "[t]he success of preclinical animal data has set the stage for a limited, early phase clinical trial using autologous BMSCs for intravenous administration to patients with stroke." Applicants respectfully submit that cell therapy in rodents is clearly reasonable predictive of human therapy, as the artisan would not understand that such human clinical trials would be undertaken on this basis absent some reasonable expectation of success. Applicants further note that evidence of successful clinical trial results in humans is not required to demonstrate enablement of a therapeutic method.

The Examiner further alleged that the skilled artisan can only draw one conclusion from the Bartley *et al.* reference cited in the Office Action of June 3, 2005, namely that somatic cell therapy with stromal cells is not reasonable predictive of therapy in humans at the time of the Applicants' filing date. Particular concerns raised by the Examiner in view of Bartley *et al.* include problems with methods involving intravenous administration, the use of undifferentiated cells, and the ability of introduced cells to survive/proliferate, particularly in the event of immune responses from the patient.

Applicants respectfully submit that the Bartley *et al.* is not germane with respect to the enablement of the presently claimed methods. Applicants first note that Bartley *et al.* only specifically examines one disease, the rarest form of cerebral palsy, while describing numerous examples of successful uses of methods similar to those presently claimed.

Applicants also respectfully submit that the post-filing references described by Bartley *et al.* further evidence the fact that the presently claimed method was fully enabled at the time of filing, such that the skilled artisan could clearly have successfully practiced the claimed methods without undue experimentation. Bartley *et al.* provide several examples of bone marrow stromal cell transplantation in which the stromal cells differentiate into cells of the nervous system, as well as the successful therapeutic intervention in rodents, particularly for stroke injury models. Specifically, Bartley *et al.* describes examples of bone marrow stromal cell differentiation to neuroprogenitor cells by Mezey *et al.*, *PNAS USA* 100:1364-1369 (2003); differentiation to cells of neuronal characteristics by Li *et al.*, J. *Cerebral Blood Flow Metal.* 20:1311-1319 (2000); differentiation to myelin producing cells by Akiyama *et al.*, *J. Neuroscience* 22:6623-6630 (2002); and differentiation into neurons by Hess *et al.*, *Stroke* 33:1362-1368 (2002). Moreover, the bone marrow stromal cells in the examples described above were all administered by methods known in the art, including direct injection, as presently claimed. Thus, these examples demonstrate the enablement of the presently claimed methods.

Furthermore, Bartley *et al.* cites numerous examples of the successful therapeutic use of transplanted bone marrow stromal cells in the treatment of neurological disease or injury, essentially practiced according to the presently claimed methods. Li *et al.* demonstrate that bone marrow stromal cells transplanted into the striatum of mice four days after middle cerebral artery occlusion demonstrate improvement on rotarod tests and a functional neurological score. In addition, Zhao *et al.* describe the implantation of human bone marrow stromal cells into rat cortex following infarction, demonstrating differentiation into cells expressing astrocyte, oligodendrocyte, or neuronal markers, and improved limb function (*Exp. Neurol.* 174:11-20 (2002)). Chen *et al.* demonstrate that while only a small number of bone marrow stromal cell-derived neurons appeared in rat brains following middle cerebral artery occlusion and intravenous administration of bone marrow stromal cells at one or seven days after the injury, the rats nevertheless demonstrated significant improvement in somatosensory behavior and neurologic severity score (*Stroke* 32:1005-1011 (2001)). This result highlights the importance of the administration of the bone marrow stromal cells to achieve therapeutic benefit, regardless of the number or identity of cells surviving. Finally, Bartley *et al.* explicitly states that data in

animals strongly suggests that human treatment may be beneficial (page 546, last sentence in first paragraph). The skilled artisan would clearly understand this to mean that the positive results described demonstrated in various animal models indicate that such methods could be reasonable expected to also prove therapeutic in humans.

With respect to the Examiner's concern that immune response would be generated from administration of bone marrow stromal cells to a patient, this is rendered moot by the present amendment to claim 1, which recites that the donor cells are syngeneic to the patient. The skilled artisan would appreciate that cells from a syngeneic source would carry the same immunological markers as the patient and, therefore, not generate an immune response.

Applicants also submit that the optimization of dosages and practice of the claimed methods in humans does not require undue experimentation by the skilled artisan. The administration of bone marrow stromal cells to the brain would be well known to one of ordinary skill in the art. The skilled artisan would necessarily be familiar with neurosurgical techniques, including injection, required to administer cells to the brain and, thus, the disclosure in the specification regarding routes of administration is fully enabling. The skilled artisan is also familiar with translating dosages from animals to humans and, as such, this requires merely routine experimentation, particularly in light of the guidance provided by the instant specification and claims, including, *e.g.*, at paragraphs 105-108. Thus, Applicants respectfully submit that the as-filed specification, coupled with the knowledge available to the skilled artisan at the time of filing, would clearly enable the skilled artisan to practice the presently claimed methods without undue experimentation.

In view of the above amendments and remarks, including the numerous references citing the predictability of human outcome based upon rodent models, as well as the numerous references evidencing the therapeutic success of the claimed methods, Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

/Carol D. Laherty/
Carol D. Laherty, Ph.D.
Registration No. 51,909

CDL:jjl

701 Fifth Avenue, Suite 5400
Seattle, Washington 98104
Phone: (206) 622-4900
Fax: (206) 682-6031

1042798_1.DOC